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Commentary

Serotonin syndrome: a clinical review of current controversies

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Serotonin syndrome is a state of increased central and peripheral serotonin (5-hydroxytryptamine) activity. Unless recognized and treated early, serotonin syndrome can lead to seizures, shock and death. Both substances with direct and indirect serotonergic activity can precipitate the syndrome. Serotonin syndrome can occur not only in psychiatric but also in non-psychiatric settings. Yet, clinicians may not be familiar with the condition. We explore some of the current controversies regarding serotonin syndrome. Specifically, we tested the following assumptions: (i) Despite being rare, serotonin syndrome is still clinically relevant; (ii) The Hunter criteria are the gold standard for diagnosing serotonin syndrome; (iii) Hyperthermia is common in cases of serotonin syndrome; (iv) Serotonin syndrome usually develops fast; (v) Severe serotonin syndrome usually or almost exclusively involves monoamine oxidase inhibitors. We found that (i) despite being rare, serotonin syndrome was clinically relevant, (ii) the Hunter criteria could not be regarded as the gold standard for the diagnosis of serotonin syndrome since they missed more cases than the other two diagnostic criteria systems (Sternbach and Radomski criteria), (iii) Serotonin syndrome could occur in the absence of an elevated temperature, (iv) fast onset could not be regarded as a reliable clinical sign of serotonin syndrome, and (v) absence of monoamine oxidase inhibitors treatment did not exclude a diagnosis of serotonin syndrome. Clinicians should bear in mind that in the context of relevant drug history, serotonin syndrome may still be possible in these circumstances.

Keywords

Serotonin syndrome; diagnosis; antidepressive agents; monoamine oxidase inhibitors; signs and symptoms; neuropsychiatry

1. Introduction

Serotonin syndrome (SS) is a state of increased central and peripheral serotonin (5-hydroxytryptamine) activity. It is a toxic state, most likely caused by stimulation of $5HT_{1A}$ and $5HT_{2A}$ -receptors in the central nervous system (CNS) (Boyer and Shannon, 2005). This toxic state can lead to extreme neuromuscular hyperexcitability. Unless recognized and treated early, SS can lead to seizures, shock and death (Boyer and Shannon, 2005). Although serotonergic drugs are commonly used, SS is rare. Hence, it is not easily picked up in randomized controlled trials. Although SS can occur in psychiatric and non-psychiatric settings, physicians may not be familiar with this condition. One study from the UK showed that 85% of primary care physicians were not familiar with SS (Mackay et al., 1999). Primary care physicians often prescribe serotonergic drugs. Still, they are unlikely to witness SS in a clinic. Affected patients are much more likely to present to emergency services (Boyer and Shannon, 2005).

There is no gold-standard diagnostic test for SS. The diagnosis of SS is purely clinical. The diagnosis depends on signs and symptoms, identified through physical examination and history of exposure to serotonergic agents. There are three diagnostic criteria systems, Sternbach, Radomski and Hunter. All three criteria systems consider neuromuscular, autonomous and cognitive symptoms, albeit to a varying degree (Dunkley et al., 2003; Radomski et al., 2000; Sternbach, 1991) (Table 1). According to the developers, the Hunter criteria are superior to the Sternbach criteria (Dunkley et al., 2003). Hence, the Hunter criteria have widely been recommended as the gold standard of SS (Boyer and Shannon, 2005; Buckley et al., 2014). However, their superiority may have been substantially overstated. Therefore, we have challenged the notion that the Hunter criteria are the gold standard for the diagnosis for SS in previous work (Werneke et al., 2016).

All three criteria systems demand the presence of a serotonergic agent, without specifying this term further. The Sternbach and Radomski criteria also require the absence of a neuroleptic agent. Even this term, the respective developers did not specify further. Often, "neuroleptics" is used interchangeably with "antipsychotics". In the context of SS, this poses a dilemma with clozapine and second-generation antipsychotics, some of which act as $5HT_2$ antagonists, whereas others act as $5HT_{1A}$ agonists (Schwartz and Stahl, 2011). As Sternbach and Radomski's criteria were developed before second-generation antipsychotics became mainstream, the requirement of absence of a neuroleptic agent may be above all applied to first-generation antipsychotics except clozapine (Werneke et al., 2016). It is acknowledged that a wide range of substances may cause SS (Table 2). However, the uncer-

Table 1. Sternbach, Radomski and Hunter diagnostic criteria for the diagnosis of serotonin syndrome (Dunkley et al., 2003; Radomski et al., 2000; Sternbach, 1991).

Sternbach criteria	Radomski criteria		Hunter criteria
Co-incidence with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following features present:	Co-incidence with the addition or increase in a known serotonergic agent (to an established treatment regimen), and the development of at least four major or three major plus two minor symptoms:		In the presence of a serotonergic agent and either symptom/symptom constellation:
Mental status changes (confusion, hypomania)	*Major*	*Minor*	Spontaneous clonus
	Mental		
Agitation	Consciousness impairment	Restlessness	Inducible clonus AND [agitation
Myoclonus	Elevated mood	Insomnia	OR diaphoresis]
Hyperreflexia	Semicoma/coma		
Diaphoresis	*Neurological*		Ocular clonus AND [agitation OR
Shivering	Myoclonus	Uncoordination*	diaphoresis]
Tremor	Tremor	Dilated pupils	
Diarrhea	Shivering	Akathisia	Tremor AND hyperreflexia
Incoordination*	Rigidity	Hyperreflexia	Hypertonic AND temperature >
Fever	*Vegetative*		38 °C AND [ocular clonus OR
	Fever	Tachycardia	inducible clonus]
	Sweating	Tachy-/dyspnea	
		Diarrhea	
		Hyper-/hypotension	
Other etiologies (e.g., infectious, metabolic or endocrine, substance abuse or withdrawal) have been ruled out.	*Clinical features, not an integral part of the underlying psychiatric disorder before commencing the serotonergic agent.*		
A neuroleptic drug had not been started or increased in dosage before the onset of the signs and symptoms listed above.	*Other etiologies (e.g., infectious, metabolic or endocrine, substance abuse or withdrawal) have been ruled out.*		
	A neuroleptic drug had not been started or increased in dosage before the onset of the signs and symptoms listed above.		

*Incoordination and uncoordination are used interchangeably in the literature.

tainty about SS's exact pathophysiological mechanism has led to a controversy regarding which substances exactly can precipitate SS. For instance, it has been suggested that that severe SS "usually" (Buckley et al., 2014; Isbister and Buckley, 2005) or "almost exclusively" (Foong et al., 2018; Isbister and Buckley, 2005) involves monoamine oxidase inhibitors.

2. Methods

For this review, we used three methods: (i) a literature review, (ii) calculation of the expected number of SS cases per year from published statistics concerning antidepressant use, and (iii) quantitative analysis of a database of published SS cases collated from a previously conducted systematic review (Ott et al., 2019; Werneke et al., 2016; Wikström, 2019).

2.1 Literature review

We performed a literature search using the PubMed/Medline and Web of Science databases, using the search terms "serotonin syndrome" and "serotonin toxicity", "diagnostic criteria", and "hyperthermia".

2.2 Calculation of the expected number of serotonin syndrome cases per year

To assess SS's clinical relevance, we calculated the expected number of SS cases in several countries worldwide, for whom updated statistics on antidepressant use were available from the Organization of Economic Collaboration and Development (OECD). The OECD uses defined daily doses (DDD) of antidepressants (Code N06A according to the Anatomical Therapeutic Chemical (ATC) Classification System) per 1000 inhabitants per day [1]. DDDs provide an estimate of the proportion of a population treated daily with a particular drug or drug class. For instance, a DDD of 10/1000 inhabitants per day for a particular drug can be interpreted as 1% (10/1000) inhabitants receive this particular drug each day in that year. DDDs are most useful for drugs used chronically with a good agreement between the average prescribed daily dose (PDD) and DDD (WHO) [2]. The WHO states that DDDs only give

[1] Organisation for Economic Co-operation and Development (OECD). Pharmaceutical market. Pharmaceutical consumption. Antidepressants. https://stats.oecd.org/Index.aspx?ThemeTreeId=9 [accessed October 28].

[2] World Health Organization (WHO). Essential medicines and health products. https://www.who.int/medicines/regulation/medicines-safety/toolkit_indicators/en/ [accessed October 31].

Table 2. Agents associated with an increased risk of serotonin syndrome (Boyer and Shannon, 2005; Buckley et al., 2014; Truedson et al., 2020).

Mechanism of action	Psychiatric treatments	Somatic treatments	Recreational drug use	Complementary medicine
MAO inhibition	MAO-A inhibitor- antidepressants Non-selective MAOI	Linezolid Methylene blue Isoniazid MAO-B inhibitors		
Serotonin reuptake inhibition	SSRI SNRI antidepressants or other SNRI agents such as atomoxetine TCAs Bupropion (indirect effect) Metoclopramide	Some opioids such as tramadol, pethidine (meperidine), pentazocine dextromethorphan Metoclopramide Valproate* Carbamazepine* Other SNRIs such as sibutramine (weight control or milnacipran (fibromyalgia)	MDMA (Ecstasy)[$]	
Serotonin release:	Amphetamines and amphetamine derivates as central stimulants	Levodopa, carbidopa-Levodopa (indirect effect)	Fenfluramine (appetite suppressor), recreational stimulants	
Other/unspecified mechanisms leading to increased serotonin activity	Lithium Buspirone	Fentanyl Ergotamine	LSD	St John's wort[&] SAMe Tryptophan Panax Ginseng
Unclear/debated whether associated with increased SS risk	Triptans Mirtazapine $5HT_2$ -blocking antipsychotics Setrones as $5HT_3$-blocking agents			

*Used also as a mood-stabilizer in a psychiatric context

[$]Stimulates also serotonin release

[&]Possibly some SSRI activity 5HT: 5-hydroxytryptamine; LSD: Lysergic acid diethylamide; MAOI: Monoamine oxidase inhibitors; MDMA: 3,4-Methylenedioxymethamphetamine; SAMe: S-adenosylmethionine; SS: serotonin syndrome; SSRI: serotonin reuptake inhibitor(s); SNRI: serotonin-noradrenaline reuptake inhibitor(s); TCA: tricyclic antidepressant.

"a rough estimate of consumption and not an exact picture of actual use" [3]. The WHO endorsed the ATC/DDD methodology for global use in 1996 as an international standard for drug utilization studies [3].

Our estimate for the incidence of SS was based on US insurance claims data collated between 2008 and 2013 from two national datasets, (i) the Veterans Health Administration (VHA) dataset and (ii) the Intercontinental Marketing Services PharMetrics Plus (IMS) dataset (Nguyen et al., 2017). To determine the minimum and the maximum number of SS cases to be expected, we used the maximum and minimum incidence figures for 2013. We multiplied these with the estimated number of patients per year taking antidepressants.

2.3 Quantitative analysis of a database of published cases

To establish the causes of severe SS, we used our database of SS cases obtained from a systematic review of cases published on PubMed/Medline or Web of Science between 1 January 2004 and 31 December 2018. We used 1 January 2004 as a starting point because all three diagnostic criteria systems for SS had become available by that time. We used the search terms "serotonin syndrome" or "serotonin toxicity" to identify cases. We counted as severe cases that had either resulted in (i) intensive care, (ii) intubation, (iii) coma, or (iv) death. We analyzed the following variables: (i) symptoms associated with severe SS, (ii) speed of onset of SS, and (iii) substances thought to have precipitated severe SS. For a potential association between monoamine oxidase inhibitors (MAOI) and severe SS, we also calculated odds ratios (OR) and 95% confidence intervals (CI). The systematic review method underlying this database has been published in detail elsewhere (Ott et al., 2019; Werneke et al., 2016; Wikström, 2019).

3. Results

3.1 Despite being rare, SS is still clinically relevant

The prevalence of SS remains unknown. Our best estimates stem from a US insurance claims study. In this retrospective cohort study of 15 million patients exposed to at least one serotonergic agent, the incidence for SS lay between 0.9 and 2.3/1000 individuals exposed in 2013 (Nguyen et al., 2017). The absolute number of cases may vary widely across the world, depending on the population size of a respective country. For instance, each year, there may only be three to six cases in Latvia, a country with a small population and low antidepressant use. However, there may be hundreds or up to a thousand cases per year in countries with large populations and/or high antidepressant use, such as Turkey, Germany or Canada (Table 3). Therefore, although SS is rare in relative terms, the number of cases can be substantial in absolute terms. This makes SS a clinically relevant condition.

3.2 The Hunter criteria are the gold standard for diagnosing SS

Our updated systematic review of published SS cases expanded our database from 299 to 412 cases collated from 350 articles. Of all 412 cases, 42% (173) had resulted in severe SS. Of all 173 severe cases, 13% (22) resulted in death. Our updated database's reanalysis showed that of all 412 SS cases, the Hunter criteria would have missed 37%. The Sternbach criteria would have missed 10%, and the Radomski criteria 24%. Of all 173 severe cases, the Hunter criteria would have missed 36%, and the Sternbach criteria would have missed 8% and the Radomski criteria 11%. In terms of missing cases SS overall and severe SS cases, the Hunter criteria performed worse than the Sternbach and Radomski criteria.

3.3 Hyperthermia is common in cases of SS

Our updated systematic case review, including only the 234 cases for whom a temperature was explicitly mentioned, 36% did not have a temperature $> 38\,^{\circ}$C (100.4 $^{\circ}$F). Of the 128 severe cases with a temperature explicitly mentioned, 27% did not have a temperature $> 38\,^{\circ}$C (100.4 $^{\circ}$F). Hence, SS can occur in the absence of an elevated temperature, even in severe course cases.

3.4 SS usually develops fast

Information on the onset speed was available for 314 of the 412 cases in the total sample and 122 of the 173 severe cases. Of the 314 cases in the total sample, 115 concerned surgical procedures, trauma care, overdoses or substance misuse and 199 concerning medical or psychiatric treatments. In the 115 cases relating to surgical procedures, trauma care, overdoses or substance misuse, 51% of all SS episodes presented within six hours and 17% after 24 hours. In the 199 cases relating to medical or psychiatric cases, 12% of all SS episodes presented within six hours and 65% after 24 hours. Of the 122 severe SS cases, 75 concerning surgical procedures, trauma care, overdoses or substance misuse and 47 concerning medical or psychiatric treatments. In the 75 severe cases relating to surgical procedures, trauma care, overdoses or substance misuse, 60% of all SS episodes presented within six hours and 9% after 24 hours. In the 47 severe cases relating to medical or psychiatric cases, 11% of all SS episodes presented within six hours and 62% after 24 hours. Our findings suggest that the speed of onset seems to depend on pharmacokinetic and pharmacodynamic factors. Therefore, fast onset cannot be regarded as a reliable clinical sign of SS.

3.5 Severe SS usually or almost exclusively involves MAOI

We explored this further using our updated systematic case review. We identified the top ten causes of severe SS as associated with any of the three diagnostic criteria systems and determined MAOI involvement for each cause. Of the 173 severe SS cases diagnosed by *any* of the three diagnostic criteria systems, only 41% (71) involved MAOI (Table 4). The odds ratio for MAOI involvement was 3.68 (CI 2.32-5.83; $P < 0.001$). As expected, most cases related to non-selective or selective MAOI-A inhibitors. Thus, our data confirm that MAOI is indeed significantly more frequently implicated in severe SS. But the absence of MAOI treatment does not exclude a diagnosis of SS.

4. Discussion

In this review, we have challenged five commonly held assumptions about serotonin syndrome. We showed that (i) despite being rare, SS was still clinically relevant, (ii) the Hunter criteria could not be regarded as the gold standard for the diagnosis of SS since they missed substantial numbers of cases, (iii) SS could occur in the absence of an elevated temperature, (iv) fast onset could not be regarded as a reliable clinical sign of SS, and (v) absence

[3] World Health Organization (WHO). Defined Daily Dose (DDD). https://www.who.int/toolkits/atc-ddd-toolkit/about-ddd [accessed December 8].

Table 3. Antidepressant use (ACT code N06A) and expected number of cases of serotonin syndrome per year (Nguyen et al., 2017).

Country	Antidepressant users in % of the population[a]	Population size in millions	Patients using antidepressants (×1000)	Expected number of cases of serotonin syndrome based on incidence number/1000 exposed to serotonergic agents[b]	
				Minimum	Maximum
Turkey	9.9	83.1	8202.0	615	1572
Germany	5.7	83	4697.8	352	900
Canada[c]	12.2	37.6	4575.9	343	877
Spain[d]	8.0	46.9	3770.8	283	723
France	5.0	67	3336.6	250	640
United Kingdom	4.4	66.7	2941.5	221	564
Italy[e]	4.3	60.4	2567.0	193	492
Australia[f]	11.2	25	2805.0	210	538
Portugal	12.4	10.3	1277.2	96	245
Korea (South)	2.1	51.7	1085.7	81	208
Sweden	10.3	10.2	1047.5	79	201
Chile	5.2	18.7	972.4	73	186
Belgium	8.0	11.5	916.6	69	176
Netherlands	4.7	17.3	820.0	62	157
Czech Republic	6.1	10.7	657.0	49	126
Greecef	6.1	10.7	652.7	49	125
Austria	6.1	8.8	539.4	40	103
Denmark	7.6	5.8	439.1	33	84
Finland	7.5	5.5	411.4	31	79
Israel	5.4	8.9	478.8	36	92
New Zealand	7.3	4.9	356.7	27	68
Norway	5.7	5.3	303.2	23	58
Hungary	3.0	9.8	289.1	22	55
Slovak Republic	4.1	5.5	226.1	17	43
Slovenia	6.2	2.1	129.2	10	25
Lithuania	3.1	2.8	87.6	7	17
Iceland	14.8	0.4	59.0	4	11
Estonia	3.5	1.3	45.2	3	9
Latvia	1.8	1.9	33.8	3	6
Luxembourg[f]	5.5	0.6	33.2	2	6

[a] As reported by the Organization for Economic Cooperation and Development (OECD), estimated from defined daily dose (DDD) /1000 inhabitants per day. https://stats.oecd.org/Index.aspx [accessed October 28].

[b] Estimated by Nguyen et al. 2017: Minimum incidence: 0.9/1000 , maximum incidence: 2.3/1000

[c] Provisional

[d] Break in statistical time series. Such occurs when there is a change in the standards for defining and observing a variable over time.

[e] Estimate

[f] Difference in methodology

of MAOI treatment did not exclude a diagnosis of SS.

4.1 The origin of the three diagnostic criteria sets for serotonin syndrome

To understand why the Hunter criteria achieved gold standard status for the diagnosis of SS, it is helpful to recall how all three diagnostic criteria systems came about. The Sternbach criteria were developed in 1991, based on 38 psychiatric cases (Sternbach, 1991). In 2000, Radomski et al. (2000) suggested a new classification building on Sternbach criteria. They expanded the underlying evidence to 62 cases, adding 24 further published cases. They also suggested that symptoms should be divided into major and minor symptoms. Radomski et al. (2000) added rigidity (hypertonicity) as a major criterion and insomnia, dilated pupils, tachycardia, tachy- or dyspnea, diarrhea, and hyper- hypotension as minor criteria. Uncoordination was another minor symptom in Radomski criteria, corresponding to the criterium of incoordination in the Sternbach criteria. Radomski et al. (2000) recognized that SS varied in severity and might manifest itself as mild, full-blown and toxic states. A third classification system, the Hunter criteria, was proposed in 2003. The Hunter criteria were derived from 473 cases of single serotonin-reuptake inhibitor (SSRI) overdoses. The derived criteria were then tested (validated) on 2222 cases of overdoses with *any* serotonergic drug. Prior to the validation exercise, rigidity was added as an additional symptom. The

Table 4. Top ten reasons for severe serotonin syndrome and the involvement of MAOI.

Cause	% accounting for all severe cases	% attributable to MAOI for each of the ten causes
	Severe serotonin syndrome *n = 173*	
Non accidental overdose	24.3	26.2
Combination of an antidepressant with methylene blue	15.6	100.0
Combination of an antidepressant with other psychiatric or somatic drugs	15.0	19.2
Combination or swap of antidepressants, start or increase in dose	9.8	29.4
Combination of an antidepressant with opiate	9.2	6.3
Combination of an antidepressant with linezolid	8.7	100.0
Substance misuse involved	6.9	8.3
Opiates or other combinations involving opiates	2.9	0.0
Other drugs combinations involving linezolid or methylene blue	2.3	100.0
Addition of antipsychotics with partial $5HT_{1A}$ agonistic effect or withdrawal of antipsychotics with $5HT_{2A}$ antagonistic properties or swap between antipsychotic substances with such properties	2.3	25.0

MAOI: monoamine oxidase inhibitors; 5HT: 5-hydroxytryptamine (serotonin).

Hunter criteria firmly shifted SS's focus to neuromuscular symptoms, particularly to clonus in various forms (Dunkley et al., 2003).

4.2 Taking diagnostic criteria to the test

The variability of symptoms between the three diagnostic systems has raised which system is the best. One major concern of the Sternbach criteria has been their potentially low specificity. For instance, a possible symptom constellation could consist of mental status changes, agitation and fever. This constellation is commonly found in many medical conditions. Yet, it is important to remember that the Sternbach criteria require the presence of a serotonergic agent, absence of a neuroleptic agent and the ruling out of other possible etiologies.

According to their developers, the Hunter criteria have better sensitivity and specificity than the Sternbach criteria (Dunkley et al., 2003). Therefore, the Hunter criteria have widely been recommended as the gold standard of SS (Boyer and Shannon, 2005; Buckley et al., 2014), but their sensitivity and specificity may have been substantially overstated. The derivation dataset, from which the Hunter criteria were generated, was also part of the validation data set, on which the Hunter criteria then were tested. 21% of all cases in the validation dataset had also been used to derive Hunter criteria. Given the magnitude of potential bias, the claim that Hunter criteria were more sensitive (84% vs. 75%) and more specific (97% vs. 96%) (Dunkley et al., 2003) than Sternbach criteria cannot be upheld (Werneke et al., 2016). Only re-analysis of the original validation set with the derivation cases' exclusion could unambiguously settle this question. The developers of the Hunter criteria themselves point out that their criteria would require validation in other settings (Dunkley et al., 2003). This, to our knowledge, has not occurred. Another concern is the exclusive reliance of Hunter criteria on overdoses for derivation and validation. In overdoses, symptoms are likely to be much more clear-cut and severe. Other cases with more discrete symptoms may be missed (Werneke et al., 2016). The Hunter criteria requirement of the presence of clonus in its various forms or a combination of tremor and hyperreflexia for SS diagnosis may also be too narrow. For instance, patients who have developed substantial rigidity may have become too constrained in their ability to move (Boyer and Shannon, 2005). Clonus and hyperreflexia may not be visible in patients in whom peripheral polyneuropathy masks upper motor neuron signs (Prakash et al., 2014).

There is substantial variability of symptoms sampled in the three classification systems. Of all symptoms, five symptoms appear in all three criteria sets. Seven are shared by two of the three criteria sets. Six symptoms are only found in one of either diagnostic criteria set. In our previous systematic review of 299 SS cases, we showed that agreement beyond chance lacked between the Hunter and Sternbach criteria and between the Hunter and Radomski criteria (Werneke et al., 2016).

4.3 Understanding the core symptoms of serotonin syndrome

Some symptoms, such as clonus, myoclonus and hyperthermia, require particular attention since their definitions can be ambiguous.

4.3.1 Clonus or myoclonus?

Clonus, the defining symptom of Hunter's criteria, is not included in the other two systems. The Sternbach and Radomski criteria list myoclonus instead (Radomski et al., 2000; Sternbach, 1991). Sometimes, the terms "clonus" and "myoclonus" are used interchangeably and incorrectly. Both symptoms are an expression of neuronal hyperexcitability. Yet, they are not the same. Myoclonus relates to brief, sudden contractions of agonist and antagonist muscles. Such can originate at any level of the CNS (Lozsadi, 2012). Clonus, however, relates to rhythmic muscle contraction as an exaggerated stretch reflex. The cause of clonus is unknown but tends to be associated with upper motor neuron lesions and hyperreflexia (Boyraz et al., 2016; Zimmerman et al., 2020). In practice, both myoclonus and clonus are often referred to as "jerks". This highlights the need to describe symptoms accurately and correctly. If "strange jerking movements" are interpreted as clonus, a case

Table 5. Commonly used monoamine oxidase (MAO) inhibitors by subtype, selectivity and reversibility.

Substance	Use	Isoenzyme		Selective	Reversible
		MAO-A	MAO-B		
Phenelzine	Antidepressant	yes	yes	yes	no
Tranylcypromine	Antidepressant	yes	yes	yes	no
Isocarboxazid	Antidepressant	yes	yes	yes	no
Moclobemide	Antidepressant	yes	no	yes	yes
Metaxalone	Muscle relaxant	yes	no	no?*	yes?*
Linezolid	Antibiotic	yes	yes	no	yes
Methylene blue	Contrast dye Treatment of Methemoglobinemia Treatment of ifosfamide toxicity	yes	no	yes	yes
Selegiline	Parkinson's disease	no	yes	yes	no
Rasagiline	Parkinson's disease	no	yes	yes	no
Safinamide	Parkinson's disease	no	yes	yes	yes

*Not clear from the literature.

may meet Hunter's criteria. If "strange jerking movements" are interpreted as myoclonus, though, a case may meet the Sternbach or Radomski criteria, but not the Hunter criteria.

4.3.2 Elevated body temperature - the cut-off point

There is no single cut-off point for elevated body temperature. Body temperature is subject to individual variability. The temperature recorded may also depend on the measurement method and timing. Rectal temperature tends to be about 0.5 °C (0.9 °F) higher than an oral temperature (Bijur et al., 2017). Afternoon temperature may, on average, be 0.3 °C (0.5 °F) higher than morning temperature (Harding et al., 2019). In women, ovulation also increases temperature between 0.28 °C (0.5 °F) and 0.56 °C (1.0 °F) in the second half of the menstrual cycle (Shilaih et al., 2018). Environmental factors may also change body temperature. A large study of 35488 patients presenting at a routine outpatient appointment examined the variability of normal body temperature. Patients presenting out of hours, suffering from an infection or receiving antibiotics were excluded. In this study, the mean temperature was 36.6 °C (97.9 °F), with a 95% range from 35.7 °C (96.3 °F) to 37.3 °C (99.1 °F), and a 99% range from 35.3 °C (95.5 °F) to 37.7 °C (99.9 °F) (Obermeyer et al., 2017). The Sternbach criteria and Radomski criteria do not give a cut-off point for elevated temperature (Radomski et al., 2000; Sternbach, 1991). The Hunter criteria refer to a temperature $>$ 38 °C (100.4 °F) (Dunkley et al., 2003). The problem of temperature definition also arises in the context of severe SS. Again, the Sternbach and Radomski criteria do not offer any cut-off point (Radomski et al., 2000; Sternbach, 1991). Radomski et al. (2000) suggest that in severe states, the temperature can exceed 40 °C (104 °F). In their discussion of the Hunter criteria, Dunkley et al. suggest that a temperature $\geq$ 38.5 °C (101.3 °F) indicates severe serotonin toxicity (Dunkley et al., 2003). Finally, Boyer and Shannon (2005) suggest core temperatures as high as 40 °C (104 °F) in SS of moderate severity. In life-threatening cases, core temperatures of $\geq$ 41.1 °C (106 °F) may occur.

4.3.3 Elevated body temperature - fever, hyperpyrexia or hyperthermia?

Elevated temperature is not only a matter of degree but also of nature. Generally speaking, core temperature is regulated by the hypothalamus. Still, causes for elevated temperature may differ. Two pathophysiological mechanisms lead to elevated body temperature. *Hyperpyrexia* refers to a high body temperature in the context of a pyrogen-mediated upregulation of the hypothalamic thermostat. Pyrogens, such as bacterial lipopolysaccharides, interleukin 1 or tumor necrosis factor α induce prostaglandin E2. These pyrogens raise the temperature set-point in the anterior hypothalamus. *Hyperthermia*, however, does not involve any pyrogens. Hyperthermia is a state of uncontrolled heat production and/or impaired heat dissipation without any upregulation of the hypothalamic thermostat (Rehman and deBoisblanc, 2014). Whether the elevated temperature is due to hyperpyrexia, i.e., high fever, or hyperthermia is not only theoretical but also of practical relevance. It is crucial for the choice of method for temperature reduction.

In SS, the elevated temperature is thought to arise from uncontrolled heat production, i.e., hyperthermia. Here, the hyperthermia is thought to be due to increased muscle activity. This results from hyperexcitability and direct serotonergic effects on the muscle (Boyer and Shannon, 2005; Rehman and deBoisblanc, 2014; Wappler et al., 2001). The $5HT_2$ receptor's role has been suggested since $5HT_2$ antagonists have been shown to prevent hyperthermia in animal experiments (Isbister and Whyte, 2002). As pyrogens are not at play, the elevated temperature may not be reducible by antipyretic drugs. Instead, treatment requires physical cooling measures.

The term fever, albeit confined to hyperpyrexic states, is often used loosely. For instance, Sternbach (1991) uses the term "fever" for his criteria. Contextually though, it becomes clear hyperthermia is meant. Radomski et al. (2000), building on the Sternbach criteria, also refer to fever. The Hunter criteria refer to a temperature $>$ 38 °C (Dunkley et al., 2003). Notably, the absence of hyperthermia does not exclude SS.

4.4 Time to onset: fast or slow?

It has been generally accepted that-SS develops fast (Boyer and Shannon, 2005). In our previous work, we have already put this claim in question (Werneke et al., 2016). Our results show that the speed of onset of SS depends on drug administration and dose. SS may develop fast in the context of overdoses or in surgical or intensive care settings, in which serotonergic agents may be administered quickly. SS may develop slowly in medical and psychiatric settings, in which serotonergic drugs are often slowly introduced or cross-tapered.

4.5 Substances associated with serotonin syndrome

All three diagnostic criteria systems require the presence of a serotonergic agent without giving a specific definition (Dunkley et al., 2003; Radomski et al., 2000; Sternbach, 1991). Pragmatically, a serotonergic agent may be defined as a substance capable of leading to excess serotonin activity (Boyer and Shannon, 2005). Sternbach (1991) and Radomski et al. (2000) suggested that SS might be due to activation of the central $5HT_{1A}$ receptor based on animal experiments findings. Other evidence from animal experiments has pointed towards $5HT_{2A}$ agonism (Isbister and Whyte, 2002; Nisijima et al., 2000). This is further supported because cyproheptadine, an antihistamine with strong $5HT_2$ antagonistic effects (Kapur et al., 1997), is recommended for the treatment of SS (Boyer and Shannon, 2005). This implies that the *withdrawal* of substances with $5HT_2$ antagonistic properties could also cause SS (Harmouche, 2018; Stevenson et al., 2013). Ultimately though, no single receptor seems to be responsible for the development of SS (Boyer and Shannon, 2005). Serotonin toxicity may be caused by an increase in serotonin's intrasynaptic concentration in the central nervous system (CNS) (Dunkley et al., 2003).

Clinicians may associate serotonergic drugs with mainly psychiatric treatments. However, many other substances also have serotonergic properties, including somatic medicines, recreational drugs and complementary remedies (Table 2) (Boyer and Shannon, 2005; Buckley et al., 2014; Truedson et al., 2020). For instance, some opiates, such as pethidine (meperidine) and tramadol, can inhibit serotonin reuptake. Not only some antidepressants but also several somatic medicines can act as MAOI, either type A or type B. Examples of MAOI-A include methylene blue and linezolid. Methylene blue is used to treat methemoglobinemia and as a contrast dye used in specific surgical procedures. Linezolid is used as an antibiotic against methicillin-resistant Staphylococcus aureus (MRSA). Examples of MAOI-B include selegiline (L-deprenyl), rasagiline, and safinamide to treat Parkinson's disease.

4.6 Severe serotonin syndrome and monoamine oxidase inhibitors

In our results, we have challenged the assumption that severe SS "usually" (Buckley et al., 2014; Isbister and Buckley, 2005) or "almost exclusively" (Foong et al., 2018; Isbister and Buckley, 2005) involves MAOI. MAOI are classified according to three pharmacological criteria, (i) affinity to subtype of the enzyme (isoenzyme), (ii) selectivity, and (iii) reversibility (Table 5). There are two forms of MAO, MAO-A and MAO-B. Both MAO-A and MAO-B metabolize dopamine and tyramine. However, MAO-A is relatively selective for the metabolism of norepinephrine and serotonin (Lotufo-Neto, 1999) with an about ten-fold higher affinity for serotonin than MAO-B (Finberg, 2014). Reversibility refers to the ease with which the MAOI can be displaced from the enzyme. Irreversible MAOI cannot be displaced from the enzyme. They essentially stay put for the lifetime of the molecule of about 14 to 28 days and deactivate the enzyme during this time (Lotufo-Neto, 1999). Reversible MAOI may clear the enzyme within a day. For instance, for moclobemide, a reversible MAOI-A, MAO-A inhibition rises to 80% within two hours of administration and lasts between eight and ten hours. After 24 hours, the MAO-A activity is completely restored. Judged on the pharmacological properties alone, irreversible MAOI with a high affinity for MAO-A, irrespective of selectivity, will carry the highest risk of SS, followed by reversible MAOI-A. Reversible MAOI-B should carry the lowest risk of SS.

Despite non-selective and selective MAOI-A having strong serotonergic properties, there is no logical reason why other serotonergic drugs could not cause SS. Neither were the three diagnostic criteria exclusively derived from MAOI. In the original 38 Sternbach criteria cases, 85% involved MAOI. However, the Hunter criteria were derived from single SSRI overdoses with any cases due to other serotonergic drugs being expressly excluded. The Hunter criteria added rigidity prior to the validation to not miss severe cases with rigidity in whom clonus or hyperreflexia was not demonstrable (Dunkley et al., 2003). These may most likely have included some SS cases caused by MAOI. Generally, SS may occur when levels of serotonin rise. Levels can rise with dose increases, the addition of serotonergic drugs or withdrawal of serotonin antagonists. Hyperserotonergic states can even arise with impairment of metabolism (e.g., via cytochrome P 450 system) or elimination (Ott et al., 2019).

5. Conclusions

The diagnosis of SS is based on clinical symptom constructs rather than an objective gold standard. Our understanding of the pathophysiological mechanism behind SS remains limited. As SS is rare, it is challenging to study. The three currently available diagnostic criteria systems only partly overlap and agree with each other. More work is needed to improve the method for diagnosing SS to increase sensitivity and specificity. Higher sensitivity minimizes false negatives and hence the likelihood of missing SS and its potentially life-threatening consequences. Higher specificity minimizes false positives so that clinicians do not unnecessarily withhold medications patients need. Equally, our current limited understanding of the underlying pathophysiology has led to a controversy concerning the substances that could cause SS. Serotonergic substances other than MAOI may more frequently be involved than commonly suggested. Clinicians should bear in mind that in the context of relevant drug history, SS may still be a differential diagnosis even (i) it is a rare occurrence, (ii) the Hunter criteria are not met, (iii) there is no elevated temperature, (iv) the onset is slow, and (v) MAOI are not involved.

Author contributions

UW and MO: conception and design of the work. PTM, HW, UW and MO: acquisition and analysis of data. UW and PTM: drafting the work. PTM, HW, MO and UW: revising and providing the final approval of the work.

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Conflict of Interest

The authors declare no conflict of interest.

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References

Bijur, P. E., Shah, P. D. and Esses, D. (2017) Temperature measurement in the adult emergency department: oral, tympanic membrane and temporal artery temperatures versus rectal temperature. *Emergency Medicine Journal* **33**, 843-847.

Boyer, E. W. and Shannon, M. (2005) The serotonin syndrome. *New England Journal of Medicine* **352**, 1112-1120.

Boyraz, I., Uysal, H., Koc, B. and Sarman, H. (2016) Clonus: definition, mechanism, treatment. *Medicinski Glasnik* **12**, 19-26.

Buckley, N. A., Dawson, A. H. and Isbister, G. K. (2014) Serotonin syndrome. *British Medical Journal* **348**, g1626-g1626.

Dunkley, E. J. C., Isbister, G. K., Sibbritt, D., Dawson, A. H. and Whyte, I. M. (2003) The Hunter serotonin toxicity criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM-Monthly Journal of the Association of Physicians* **96**, 635-642.

Finberg, J. P. M. (2014) Update on the pharmacology of selective inhibitors of MAO-A and MAO-B: focus on modulation of CNS monoamine neurotransmitter release. *Pharmacology & Therapeutics* **143**, 133-152.

Foong, A., Patel, T., Kellar, J. and Grindrod, K. A. (2018) The scoop on serotonin syndrome. *Canadian Pharmacists Journal/Revue Des Pharmaciens Du Canada* **151**, 233-239.

Harding, C., Pompei, F., Bordonaro, S. F., McGillicuddy, D. C., Burmistrov, D. and Sanchez, L. D. (2019) The daily, weekly, and seasonal cycles of body temperature analyzed at large scale. *Chronobiology International* **36**, 1646-1657.

Harmouche, E. (2018) A hard stop: clozapine withdrawal causing serotonin syndrome. *Clinical Toxicology* **56**.

Isbister, G. K. and Buckley, N. A. (2005) The pathophysiology of serotonin toxicity in animals and humans. *Clinical Neuropharmacology* **28**, 205-214.

Isbister, G. K. and Whyte, I. M. (2002) Serotonin toxicity and malignant hyperthermia: role of 5-HT2 receptors. *British Journal of Anaesthesia* **88**, 603.

Kapur, S., Zipursky, R. B., Jones, C., Wilson, A. A., DaSilva, J. D. and Houle, S. (1997) Cyproheptadine: a potent *in vivo* serotonin antagonist. *The American Journal of Psychiatry* **154**, 884.

Lotufo-Neto, F. (1999) Meta-Analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology* **20**, 226-247.

Lozsadi, D. (2012) Myoclonus: a pragmatic approach. *Practical Neurology* **12**, 215-224.

Mackay, F. J., Dunn, N. R. and Mann, R. D. (1999) Antidepressants and the serotonin syndrome in general practice. *The British Journal of General Practice* **49**, 871-874.

Nguyen, C. T., Xie, L., Alley, S., McCarron, R. M., Baser, O. and Wang, Z. (2017) Epidemiology and economic burden of serotonin syndrome with concomitant use of serotonergic agents: a retrospective study utilizing two large US claims databases. *The Primary Care Companion for CNS Disorders* **19**, 17m02200.

Nisijima, K., Yoshino, T. and Ishiguro, T. (2000) Risperidone counteracts lethality in an animal model of the serotonin syndrome. *Psychopharmacology* **150**, 9-14.

Obermeyer, Z., Samra, J. K. and Mullainathan, S. (2017) Individual differences in normal body temperature: longitudinal big data analysis of patient records. *British Medical Journal* **359**, j5468.

Ott, M., Mannchen, J. K., Jamshidi, F. and Werneke, U. (2019) Management of severe arterial hypertension associated with serotonin syndrome: a case report analysis based on systematic review techniques. *Therapeutic Advances in Psychopharmacology* **9**, 204512531881881.

Prakash, S., Gosai, F., Brahmbhatt, J. and Shah, C. (2014) Serotonin syndrome in patients with peripheral neuropathy: a diagnostic challenge. *General Hospital Psychiatry* **36**, 450.e9-450.e11.

Radomski, J. W., Dursun, S. M., Reveley, M. A. and Kutcher, S. P. (2000) An exploratory approach to the serotonin syndrome: an update of clinical phenomenology and revised diagnostic criteria. *Medical Hypotheses* **55**, 218-224.

Rehman, T. and deBoisblanc, B. P. (2014) Persistent fever in the ICU. *Chest* **145**, 158-165.

Schwartz, T. L. and Stahl, S. M. (2011) Treatment strategies for dosing the second generation antipsychotics. *CNS Neuroscience & Therapeutics* **17**, 110-117.

Shilaih, M., Goodale, B., Falco, L., Kübler, F., De Clerck, V. and Leeners, B. (2018) Modern fertility awareness methods: wrist wearables capture the changes in temperature associated with the menstrual cycle. *Bioscience Reports* **38,** BSR20171279.

Sternbach, H. (1991) The serotonin syndrome. *The American Journal of Psychiatry* **148**, 705-713.

Stevenson, E., Schembri, F., Green, D. M. and Burns, J. D. (2013) Serotonin syndrome associated with clozapine withdrawal. *Jama Neurology* **70**, 1054.

Truedson, P., Ott, M., Bernberg, E. and Werneke, U. (2020) Neuroleptic malignant syndrome and serotonin syndrome - severe adverse reactions with psychotropic medications. *Lakartidningen* **117**, F3LI. (In Swedish)

Wappler, F., Fiege, M. and Schulte am Esch, J. (2001) Pathophysiological role of the serotonin system in malignant hyperthermia. *British Journal of Anaesthesia* **87**, 794-798.

Werneke, U., Jamshidi, F., Taylor, D. M. and Ott, M. (2016) Conundrums in neurology: diagnosing serotonin syndrome-a meta-analysis of cases. *BMC Neurology* **16**, 97.

Wikström, H. (2019) *The symptomatology of severe serotonin syndrome-a pooled case analysis*. Master of Medical Sciences Thesis. Umeå University, Sweden.

Zimmerman, B., Hubbard, J. B. (2020) *Clonus*. Treasure Island (FL): StatPearls Publishing.